Commentary

Preventing Bone Disease Requires Diligent Management in Patients With Renal Failure

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When we received the letter to the editor by F. I. Polsky, MD, and M. A. Fullmer, MD, elsewhere in this issue of THE WESTERN JOURNAL OF MEDICINE, *we felt it deserved a commentary. Felix Kolb, MD, has had extensive experience managing patients with complex clinical problems before and after renal transplantation.*

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Editor

The miseries of a young woman with end-stage renal disease—refractory anemia, hypertension, prolonged hemodialysis after the rejection of three renal allografts, autonomous hyperparathyroidism leading to total parathyroidectomy, the "hungry bone" syndrome, and finally, probably permanent hypoparathyroidism—described by F. I. Polsky, MD, and M. A. Fullmer, MD,[1] are reminiscent of an old motion picture serial entitled "The Perils of Pauline." The heroine encounters a series of mishaps from which she is rescued just in the brink of time.

This case report deserves comment because patients with similar complications are seen with increasing frequency in large dialysis and transplantation centers as the lives of patients with end-stage renal failure are prolonged for many years. Some of these complications (autonomous secondary hyperparathyroidism, severe renal osteitis) can be anticipated and possibly averted; others (calcinosis, aluminum bone disease) that are in part iatrogenic could be ameliorated by careful management of the patient's parathyroid function and phosphate balance.

A brief review of the genesis of these complications and their proper management seems in order.[2-4] The kidney is an active endocrine organ handling phosphate and calcium excretion and the synthesis of the active form of vitamin D, 1,25-dihydroxyvitamin D3 (calcitriol) largely under the control of parathyroid hormone. With decreasing creatinine clearance (< 0.67 ml per second [40 ml per minute]), phosphate excretion is diminished, leading to a subtle fall in ionized calcium and to parathyroid stimulation, which in turn normalizes serum phosphorus and calcium levels.

At this stage, a reasonable restriction in dietary phosphate and adequate calcium and vitamin D intake will reestablish homeostasis. As renal function declines further, phosphate retention becomes more severe, with impaired production of calcitriol and further parathyroid hyperplasia. Intermittent dialysis is now initiated. The use of aluminum-containing phosphate-binding agents in moderate doses and large amounts of either calcium carbonate or calcium acetate (calcium citrate is contraindicated because it enhances aluminum absorption)[5,6] and the addition of the active vitamin D compounds 25-hydroxycholecalciferol (calcifediol) or calcitriol will again return the serum calcium and phosphorus levels to normal and avert the development of secondary osteitis fibrosa cystica. It is imperative to monitor the serum parathyroid hormone level regularly, using the generally available immunoradiometric assay (IRMA). If the level exceeds two to three times the upper limits of normal (> 16 pmol per liter [160 pg per ml]), bone disease will occur. An admixture of osteitis and osteomalacia is usually found with progressive elevations of the serum alkaline phosphatase level. The combination of osteitis, osteomalacia, and at times also osteosclerosis and osteoporosis has been called "renal osteodystrophy" with striking changes in skeletal x-ray films and scans. To suppress severe secondary hyperparathyroidism, intermittent intravenous calcitriol is now generally used.[7] The serum phosphorus level must be carefully controlled because exceeding the solubility product of the calcium level times the phosphorus level (> 70) will lead to heterotopic calcification. There has been an increase in the incidences of both tumoral calcinosis and calciphylaxis in our patients and those at other dialysis centers, possibly related to the use of large doses of calcium carbonate and calcitriol.[8,9]

The distressing symptoms of severe pruritus, painful subcutaneous nodules with skin necrosis, and vascular calcification—which led to amputation of both legs in one of our patients—require drastic measures, including strict control of the serum phosphorus level, adjustment of the dialysate calcium, and frequently subtotal parathyroidectomy.[10]

If, despite serious attempts to control parathyroid hypersecretion, severe secondary autonomous parathyroid hyperplasia with progressive hypercalcemia (also called tertiary hyperparathyroidism) occurs, subtotal

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parathyroidectomy is required. This happened in the case reported, in which the patient had recurrence of hyperparathyroidism in the remnant gland, leading to total parathyroidectomy. While recurrent hyperparathyroidism may be due in part to poor patient compliance with medical therapy, a recent report suggests that a chromosomal change occurs in large hyperplastic parathyroids, leading to adenoma formation.[11] Parathyroid size can now be monitored by ultrasonography,[12] and recurrent hyperfunctioning parathyroid glands can now be visualized by the use of the radionuclide technetium Tc 99m sestamibi.[13] Some centers do total rather than subtotal parathyroidectomies with transplantation of a portion of one of the smaller hyperplastic glands to the forearm to lessen the "hungry bone" syndrome and avoid permanent hypoparathyroidism.

Parathyroidectomy is contraindicated in patients who have the recently recognized syndrome of aluminum osteodystrophy,[14] with adynamic or "low-turnover" bone disease, associated with severe bone pain and fractures. It can be diagnosed only by proper bone biopsy with aluminum staining, which shows aluminum at the calcification front with osteomalacia and osteoporosis.

Aluminum osteodystrophy is unresponsive to vitamin D therapy, which may actually markedly aggravate the hypercalcemia. It could represent a state of relative hypoparathyroidism because aluminum suppresses parathyroid function. Parathyroid hormone levels are generally lower than in patients with osteitis fibrosa. The removal of aluminum by deferoxamine mesylate has been useful in some patients with this disorder, but is associated with serious side effects such as mucormycotic infections.[15] Avoiding aluminum-containing phosphate binders and substituting calcium and magnesium carbonate may help these patients.[16,17]

Other complications seen in patients on long-term dialysis are amyloidosis due to the retention of microglobulins with bone cyst formation and carpal tunnel syndrome.[18] Prolonged erythropoietin therapy can cause refractory hypertension and, rarely, massive bone marrow hyperplasia with the erosion of bone, which led to pathologic hip fracture in one of our patients (R. Garcia-Kennedy, F.O.K., unpublished data, 1990). The cause of the distressing myopathy and neuropathy seen in some patients is not known, but high levels of parathormone and aluminum may be contributory factors.

Before renal transplantation is undertaken, the parathyroid and bone status should be carefully evaluated to avoid disastrous complications, such as severe hypercalcemia. Severe hyperparathyroidism and florid bone disease must be partially controlled before transplantation. After a successful transplant, the "Perils of Pauline" are not over. A new set of problems related to the return of normal renal function and the need of immunosuppression to prevent rejection of the transplant arises.[19,20]

The use of high-dose corticosteroids changes the high-turnover bone state of secondary hyperparathyroidism to a low-turnover state by suppressing osteoblast function. This can be monitored by serial serum osteocalcin (γ-carboxyglutamic acid) measurements. Corticosteroids enhance the resorption of trabecular bone. The concurrent administration of cyclosporine will partially reverse this by increasing bone turnover, but this does not occur in an organized fashion, and in general, bone disease progresses in the first year after transplantation in patients receiving steroids plus cyclosporine. Azathioprine probably has an effect similar to corticosteroids.[21] Steroid-treated patients must receive adequate amounts of calcium and vitamin D to offset the antiabsorptive action of cortisone. This is often difficult because some patients show persistent hypercalcemia and hyperparathyroidism for several months after transplantation.

Hypophosphatemia may occur with the return of normal renal function and must be treated with phosphate supplementation. Patients on steroid therapy are also subject to infections such as osteomyelitis and to osteonecrosis of joints, especially of hips, knees, and shoulders.[21,22] The early recognition of this serious disorder by bone scan and magnetic resonance imaging may avert the need for joint replacement. Cyclosporine toxicity includes hypertension, hirsutism, and severe hyperuricemia and gout requiring allopurinol therapy. In the future, the availability of noncalcemic analogues of vitamin D, such as 22-oxacalcitriol, will make it possible to treat persistent hypercalcemia more rapidly, avoiding the need for parathyroidectomy.[23]

Post-transplantation osteopenia can be monitored readily with serial measurements of bone mineral density using dual-energy x-ray absorptiometry.[24] A reduction in corticosteroid use and the administration of sex steroids, calcitonin, and the newer bisphosphonates may be needed to reverse persistent or progressive post-transplantation osteopenia.[20]

This review illustrates the complex nature of the metabolic changes seen in patients with end-stage renal disease, both before and after renal transplantation. Careful control of the parathyroid hormone level and of the calcium-phosphate product by a judicious regulation of diet, dialysate, calcitriol dose, and the early recognition of possible hazards to patients similar to those in the case reported in this issue may lessen some of their miseries and improve the quality of their lives. In our medical center, the combined efforts of nephrologists, transplant physicians, and endocrinologists have averted or greatly reduced the severity of some of these perils.

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